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INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

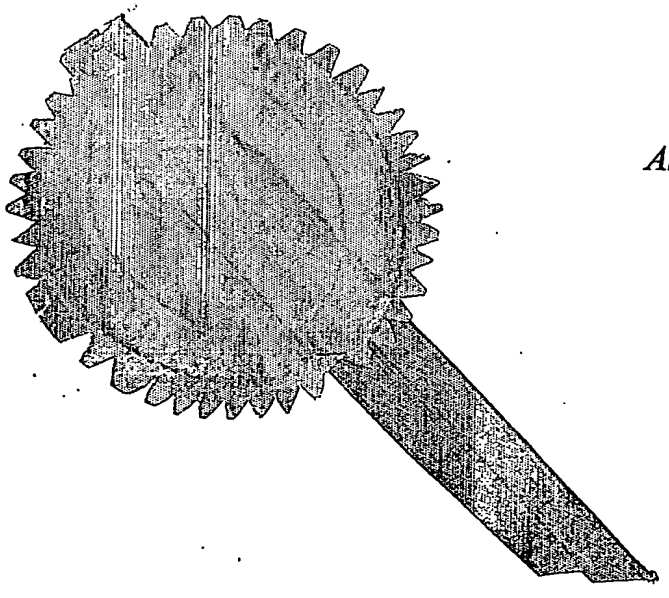
GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

REC'D 13 AUG 2004
WIPO PCT

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1156/Del/2002*** *dated* ***15th November 2002.***

Witness my hand this 6th day of July 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs



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1156 DEL 02

FORM 1

15 NOV 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS OF STABILIZING BUPROPRION HYDROCHLORIDE SOLID DOSAGE FORMS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MANISH CHAWLA

b. RAJEEV SINGH RAGHUVANSHI

c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126
Fax No. (91-124) 6342027

DUPLICATE

6. Following declaration was given by the inventors in the convention country:

We, MANISH CHAWLA, RAJEEV SINGH RAGHUVANSHI, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (MANISH CHAWLA)

b. (RAJEEV SINGH RAGHUVANSHI)

c. (ASHOK RAMPAL)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.**5,000/-** (Rupees Five Thousand only..) in cheque bearing No. **685262** dated **22.10.2002** on ANZ Grindlays Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this **14TH** day of **November,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

Vinay Kumar Kaul

RANBAXY LABORATORIES LTD. N. Delhi

1156 DEL 02
15 NOV 2002

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

A PROCESS OF STABILIZING BUPROPION HYDROCHLORIDE SOLID DOSAGE FORMS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for stabilizing bupropion hydrochloride solid dosage form using Glucono delta lactone or corresponding open chain hydroxy acid derivative.

Bupropion hydrochloride is a well-known antidepressant and a non-nicotine aid to smoking cessation. GLAXOSMITHKLINE sells it in United States as WELLBUTRIN® (bupropion hydrochloride immediate release tablets), WELLBUTRIN® SR and ZYBAN® SR (bupropion hydrochloride sustained release tablets).

Bupropion hydrochloride is a water-soluble, crystalline solid, which is highly hygroscopic and susceptible to decomposition. Because of the drug's instability, researchers working in this field have tried a number of different approaches to improve the storage stability of the drug in the formulation. Prior art patents variously cover use of organic acids, carboxylic acids, dicarboxylic acids, inorganic acids, acid salts of an amino acids, sodium metabisulfite and sodium bisulfate as stabilizers for bupropion compositions.

These prior art patents describe the use of L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulphate, citric acid, tartaric acid, L-cystine dihydrochloride, oxalic acid, succinic acid, fumaric acid, phthalic acid, hydrochloric acid, phosphoric acid, nitric acid and sulphuric acid as stabilizers in particular.

Inventors of the present invention have discovered a novel process to stabilize bupropion hydrochloride solid dosage forms with Glucono delta lactone or corresponding open chain hydroxy acid derivative. Glucono delta lactone can be added as such or in the form of corresponding open chain hydroxy acid derivative. Glucono delta lactone is a crystalline compound, which hydrolyses to the corresponding open chain hydroxy acid derivative upon contact with moisture.

Present invention therefore discloses a process for stabilizing bupropion hydrochloride solid dosage forms using Glucono delta lactone or corresponding open chain hydroxy acid derivative.

The stabilized bupropion hydrochloride dosage form herein means dosage forms retaining at least 80% of the bupropion hydrochloride potency at storage time, when stored for 3 months at 40°C and 75% relative humidity.

For the purpose of the present invention, the term "bupropion hydrochloride" refers to the hydrochloride salt of m-chloro-α- (t-butylamino) propiophenone. The amount of bupropion hydrochloride may vary from 25 to 500 mg.

Glucono delta lactone as described above can be added as such or as corresponding open chain hydroxy acid derivative i.e. gluconic acid. Addition of Gluono delta lactone is preferred due to ease of handling, sweet taste & high aqueous solubility. These stabilizers can be easily used in compositions prepared by wet granulation as well as dry granulation methods.

These stabilizers can be used in a concentration, which can effectively retain at least about 80% of the potency of bupropion hydrochloride in bupropion hydrochloride solid dosage forms after storage for three months at 40°C and 75% relative humidity. Amount of glucono delta lactone or its corresponding open chain hydroxy acid derivative may vary from 5% to 100% of weight of bupropion hydrochloride. Preferably it is about 5% to 50% of weight of bupropion hydrochloride.

Solid dosage forms of the present invention include tablets, caplets, capsules and granulates. Immediate release, modified release and extended release profiles are also included.

The stabilized dosage forms of bupropion hydrochloride can be conveniently prepared by any of the methods known to the one skilled in the art. For tablets, the method of choice can be wet granulation, dry granulation or direct compression. These methods include the basic step of intimately mixing the stabilizer with bupropion hydrochloride along with other pharmaceutically acceptable excipients and shaping the product into a solid dosage form. Alternatively, the stabilizer (either complete/part) may also be added in granulating fluid during wet granulation.

The pharmaceutical acceptable excipients of the present invention may be selected from rate controlling polymers (depending upon the choice whether an instant or sustained release composition is needed), coating polymers, diluent, binders, disintegrants, lubricants, glidants and coloring agents compatible with bupropion hydrochloride.

For the present invention, release rate-controlling polymers may be selected from any such pharmaceutically acceptable excipients, which can control the rate of release of the active ingredient. Preferably such release rate-controlling polymers can be selected from the group consisting of cellulose derivatives, acrylates, methacrylates, polyvinlyacetate/povidone mixture, polyethylene oxides, starch and their derivatives, gums, alginates, carbohydrate based polymers, polysaccharides or combinations thereof.

Cellulose derivative can be selected from the group consisting of ethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose and sodium carboxymethylcellulose of different degree of substitution and molecular weights. These release rate-controlling polymers can be used alone or in combination. Various degrees of substitution and/or different molecular weights corresponding to a different degree of viscosity can be used as suitable cellulose based rate-controlling system.

Rate controlling polymer can be used in a concentration of 5% to 60% of the tablet weight depending on the polymer used. The use of hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose, polyvinyl acetate/povidone mixture or Carboxyvinyl polymers such as Carbopol® are preferred. Upon hydration, these polymers swell to form a gelatinous barrier, through which either the drug may diffuse out or be released by erosion of the barrier or a combination of erosion and diffusion.

Diluents of this invention may be selected from any such pharmaceutically acceptable excipients, which give bulk to the composition and improve compressibility. Preferably those diluents may be selected from starch or its derivatives, microcrystalline cellulose, lactose, glucose, mannitol, alginates, alkali earth metal salts, dicalcium phosphate, glyceryl monostearate, polyvinyl acetate/povidone mixture or polyethylene glycols.

Binders of this invention may be selected from any such pharmaceutically acceptable excipients, which have cohesive properties to act as a binder. Preferably those excipients are starch, gelatin, highly dispersed silica, mannitol, lactose, polyethylene glycol, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose and natural or synthetic gums.

The disintegrant of the present invention may be selected from sodium starch glycolate, carboxy methylcellulose, croscarmellose sodium and crospovidone or combination thereof.

Lubricants of the present invention may be selected from talc, stearic acid, magnesium stearate, other alkali earth metal stearate like calcium, zinc etc., sodium lauryl sulphate, hydrogenated vegetable oil, sodium benzoate, sodium stearyl fumarate, glyceryl monostearate and PEG 4000.

Glidants of the present invention may be selected from colloidal silicon dioxide and talc.

The stability of bupropion hydrochloride compositions was tested after storage for four to twelve weeks at 40°C and 75% relative humidity. Bupropion hydrochloride compositions containing stabilizers of the present invention stored under these conditions retain at least 80% of bupropion hydrochloride in the composition. In many instances, the formulations of the present invention retain more than 85% of bupropion hydrochloride in the composition.

The present invention is further illustrative by, but is by no-means limited to, the following examples:

EXAMPLES 1 & 2: Bupropion hydrochloride 150-mg formulations

Ingredient	Weight (mg) per tablet	
	Example 1	Example 2
Bupropion hydrochloride	150.00	150.00
Hydroxypropyl cellulose	50	50
Microcrystalline cellulose	208.5	168.5
Glucono delta lactone	3.5	3.5
Polyvinlyacetate/Povidone mixture	-	40
Stearic acid	4	4
Total	416.00	416.00

The above bupropion hydrochloride formulations were prepared using the following process:

1. Bupropion hydrochloride, Hydroxypropyl cellulose, Microcrystalline cellulose, Polyvinlyacetate/Povidone mixture (in example 2) were mixed in a blender.
2. The blend of step 1 was granulated with an aqueous solution of Glucono delta lactone.
3. Granules were dried & sized accordingly.
4. Granules were lubricated with stearic acid & compressed to form tablets.

Example-3

Ingredient	Weight (mg) per tablet
Bupropion hydrochloride	150.00
Hydroxypropyl cellulose	50
Microcrystalline cellulose	168.5
Glucono delta lactone	43
Stearic acid	4
Total	416.00

Process:

1. Bupropion hydrochloride, Hydroxypropyl cellulose, a part of Glucono delta lactone & microcrystalline cellulose were mixed in a blender.
2. Aqueous solution of the remaining quantity of glucono delta lactone was used to granulate the blend of step 1.
3. The wet mass was dried in the fluid bed dryer & the granules sized.
4. Granules were lubricated with stearic acid & compressed into tablets.

Product stability data were obtained for the above formulation by storage at 40°C, 75% relative humidity for 3 months. Potency was determined using HPLC. Product stability data are presented in Table 1.

Table 1: Comparative stability of Bupropion hydrochloride tablets prepared as per the composition of Examples-1 - 3 vs commercially available bupropion hydrochloride tablets (WELLBUTRIN SR ®).

Stability conditions	% Bupropion hydrochloride*			
	EXAMPLES			WELLBUTRIN SR ®
	1	2	3	
Initial	101.6	99.7	100.1	105.3
1 month at 40°C / 75% RH	93.8	91.6	96.7	95.1
2 month at 40°C / 75% RH	88.5	83.9	99.5	89.0
3 month at 40°C / 75% RH	81.3	76.1	89.9	----

RH = Relative Humidity

* % of added quantity

The above data clearly indicates that Glucono delta lactone effectively stabilizes bupropion hydrochloride tablets.

WE CLAIM:

1. A process for stabilizing bupropion hydrochloride solid dosage forms using Glucono delta lactone or corresponding open chain hydroxy acid derivative.

2. The process according to claim 1 wherein stabilization is carried out using Glucono delta lactone.

3. The process according to claim 1 wherein stabilization is carried out using corresponding open chain hydroxy acid derivative of Glucono delta lactone.

4. The process according to claim 3 wherein corresponding open chain hydroxy acid derivative of Glucono delta lactone is Gluconic acid.

5. The process according to claim 1 wherein the concentration of Glucono delta lactone or corresponding open chain hydroxy derivative is from about 5% to about 100% by weight of bupropion hydrochloride.

6. The process according to claim 5 wherein the concentration of Glucono delta lactone or corresponding open chain hydroxy derivative is from about 5% to about 50% by weight of bupropion hydrochloride.

7. The process according to claim 1 wherein the amount of bupropion hydrochloride is 25 to 500 mg.

8. The process according to claim 1 wherein the solid dosage form is a tablet, capsule or granulate with or without immediate release, modified release and extended release profiles.

9. The process according to claim 8 wherein the solid dosage forms is a tablet.

10. The process according to claim 9 wherein tablet is a sustained release tablet.

11. The process according to claim 8 wherein the solid dosage forms is a capsule.

12. The process according to claim 11 wherein the capsule is a sustained release capsule.

13. The process according to claim 9 or 10 wherein tablet is formulated by wet granulation method.

14. The process according to claim 9 or 10 wherein the tablet is formulated by dry granulation method.

15. The process according to claim 9 or 10 wherein the tablet is formulated by direct compression method.

16. The process according to claim 1 wherein the stabilized bupropion hydrochloride solid dosage form additionally contains pharmaceutically acceptable excipients which may be selected from rate controlling polymers, diluent, binders, disintegrants, lubricants, glidants and coloring agents.

17. The process according to claim 16 wherein the release rate controlling polymers may be selected from the group consisting of cellulose derivatives, acrylates, Polyvinlyacetate / Povidone mixture, polyethylene oxides, starch & their derivatives, gums, alginates, carbohydrate based polymers, polysaccharide or combinations thereof.

18. The process according to claim 17 wherein the cellulose derivative is selected from the group consisting of ethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose or a mixture thereof.

19. The process according to claim 18 wherein the cellulose derivative is hydroxypropyl cellulose.

20. The process according to claim 16 wherein the diluent is microcrystalline cellulose.

21. The process according to claim 16 wherein the lubricant is stearic acid.

22. The process according to claim 1 wherein stabilized bupropion hydrochloride solid dosage form contain about 80% of undegraded bupropion hydrochloride after storage for three months at 40°C and 75% relative humidity.

23. A process of stabilizing bupropion hydrochloride tablets substantially as described and illustrated by the examples herein.

Dated this **14TH** day of **November, 2002.**

For Ranbaxy Laboratories Limited

Vinay Kumar Kaul

RANBAXY LABORATORIES LTD. N. Delhi

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

A PROCESS OF STABILIZING BUPROPION HYDROCHLORIDE SOLID DOSAGE FORMS

The present invention relates to a process for stabilizing bupropion hydrochloride solid dosage form using Glucono delta lactone or corresponding open chain hydroxy acid derivative.